## DETAILED ACTION

1. Claim 61 is cancelled.

Claims 1-16 and 19-20 have been amended.

2. Claims 33-58 and 63-71 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

3. Claims 1-32, 59-60 and 62 are under consideration.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. This Office Action contains New Grounds of Rejections.

***Objections/Rejections Withdrawn***

6. The rejection of claims 1-8 and 15 under 35 U.S.C. 102(b) as being anticipated by Weitzhandler et al (Journal of Pharmaceutical Sciences, 83(12):1670-1675, December 1994) as evidenced by the specification is withdrawn in view of the Declaration of John Lambert under 37 C.F.R. 1.132, providing evidenced that the My9-6 antibody was not available.

7. The rejection of claims 1-8, 15 and 17-28 under 35 U.S.C. 102(b) as being anticipated by CML NewsBytes, 10/24/2001, (www.cmlsupport.com/cmlnewsbytesarchives2.htm), as evidenced by the specification is withdrawn in view of the Declaration of John Lambert under 37 C.F.R. 1.132, providing evidenced that the My9-6 antibody was not available.

8. The objection of claims 3-4, 6-7, 9-10 and 12-13 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn in view of the amendments to the claims.

9. The rejection of claims 1-32 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation “represented by…” is withdrawn in view of the amendments to the claims.

10. The rejection of claims 4, 7, 10 and 13 under 35 U.S.C. 112, second paragraph, as lacking antecedent basis for the limitation "said amino acid" is withdrawn in view of the amendments to the claims

11. The rejection of claims 19-20 under 35 U.S.C. 112, second paragraph, as being indefinite for reciting "derivatives thereof" is withdrawn in view of the amendments to the claims.

12. The rejection of claims 1-8, 15 and 17-28 under 35 U.S.C. 102(b) as being anticipated by BioCentury Part II, vol. 9, No. 48, pp. B1-B22, October 29, 2001, as evidenced by the specification is withdrawn in view of the Declaration of John Lambert under 37 C.F.R. 1.132, providing evidenced that the My9-6 antibody was not available and in view of applicants' remarks in the reply filed 1/29/2008.

13. The rejection of claims 1-8, 15 and 17-32 under 35 U.S.C. 103(a) as being unpatentable over Goldenberg et al (U.S. Patent 6,759,045 B2, 8/8/2000, cited on PTO-892 mailed 6/14/06) in view of BioCentury Part II, vol. 9, No. 48, pp. B1-B22, October 29, 2001, as evidenced by the specification is withdrawn in view of the Declaration of John Lambert under 37 C.F.R. 1.132, providing evidenced that the My9-6 antibody was not available and in view of applicants' remarks in the reply filed 1/29/2008.

***Objections/Rejections Maintained and New Grounds of Rejections***

14. The objection of claims 5, 8, 11 and 14 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is maintained.

The response filed 8/20/2007 states that claims 3-4, 6-7, 9-10 and 12-13 have been amended solely to advance prosecution and applicants' have also amended claims 5, 8, 11 and 14 to overcome the objection. Applicants' amendments to claims 3-4, 6-7, 9-10 and 12-13 have overcome the objection applied thereto (see item no. 8 above). With respect to claims 5, 8, 11 and 14 applicants' amendment/arguments are not found persuasive. As set forth in the previous Office Action dependent claims 5, 8,

11 and 14 recite antibodies that comprise "an amino acid sequence" of the recited heavy and light chain variable regions, which encompasses fragments of the recited variable regions as few as two amino acids, since two amino acids of SEQ ID NO:7 is merely one interpretation of "an amino acid sequence" and as such does not include the CDRs recited in base claim 2. It is reiterated that any claim which is in dependent form but which is so worded that it, in fact is not, as, for example, it does not include every limitation of the claim on which it depends, will be required to be canceled as not being a proper dependent claim; and cancellation of any further claim depending on such a dependent claim will be similarly required.

For these reasons the objection is maintained.

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. The rejection of claims 3-32, 59-60, 62 and now applied to claims 1-2 as presently amended under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated antibodies and epitope-binding fragments thereof that specifically bind CD33 and comprise the heavy chain CDRs of SEQ ID Nos:1-3 and the light chain CDRs of SEQ ID Nos:4-6 or comprises the heavy chain variable region of SEQ ID NO:7 and/or the light chain variable region of SEQ ID NO:8 or comprising the heavy chain variable region of SEQ ID NO:9 and/or the light chain variable region of SEQ ID NO:10 as well as conjugates thereof and compositions comprising said isolated anti-CD33 antibodies or epitope-binding fragments thereof, does not reasonably provide enablement for all of the embodiments embraced by the claims is maintained.

Applicants' arguments have been carefully considered but are not persuasive. Applicant refers to Holt et al as disclosing domain antibodies comprising only three heavy chain CDRs that retain the binding activity of the antibody from which they were derived. Applicants' reference to Holt et al is acknowledged, however, Holt et al has not

been provided in the reply filed 8/20/07 and it is unclear where the reference can be found in the current record. Assuming that Holt teaches domain antibodies comprising only the heavy chain variable region of an antibody, it is noted that the present claims are not drawn to heavy chain antibodies and the written description of the present application does not describe these molecules which bind CD33. There is no evidence that the heavy chain of the murine My9-6 monoclonal antibody retains the CD33 binding function in the absence of the corresponding light chain variable region. Applicant also submits Aires da Silva et al, Tanaka et al and Peterson et alto educate the examiner on these issues. Applicants' references/arguments have been fully considered but are not found persuasive. While the examiner appreciates applicants' education, Aires da Silva et al and Tanaka et al are drawn to single-domain VH antibodies, however, the present claims are not drawn to VH domain antibodies and the written description in the present application do describe these VH domain antibodies. Further, while the examiner is aware that certain VH domain antibodies exist, the present application provides no direction or guidance thereto wherein the VH domain antibodies bind CD33. Peterson et al is addressed below.

Applicants again argue that Rajpal et al (PNAS, 102(24):8466-8471, 2005) provide methods to optimize binding of an antibody using antibody engineering techniques and one could test homologues of the My9-6 antibody using look through mutagenesis technology and develop a comprehensive optimization map of the antigen binding site in "facile and rapid manner" (pg. 8466, col. 2, of Rajpal). Applicant reiterates that the specification discloses procedures for making an antibody as well as assays for determining the binding characteristics. Thus, Applicants argue that the skilled artisan would be able to make variants, and then test the random variants to see if they bound the recited CD33 structure. This is not persuasive because the specification provides no guidance of which residues can be changed with a favorable binding characteristic. Further, unlike Rajpal, the claims encompass amino acid deletions and insertions (i.e., 90 and 95% sequence identity), whereas the art of Rajpal is limited to amino acid substitutions. The specification does not disclose the genus of antibody variants. The argument as essentially set forth indicates no disclosure of the

genus is necessary, no guidance to make any changes is required because the skilled artisan can make and test using art recognized techniques to discover how best to practice the claimed invention. This is not persuasive because the issue is make and use, not make and test to see if the skilled artisan could use. In short, the instant application describes a method for determining whether a given antibody possesses certain desired characteristics, and identifies some broad categories that *might work*, however, these descriptions, without more precise guidelines, amount to little more than "a starting point, a direction for further research." *Genentech*, 108 F.3d at 1366. *See also Calgene*, 188 F.3d at 1374 ("the teachings set forth in the specification provide no more than a 'plan' or 'invitation' for those of skill in the art to experiment practicing [the claimed invention]; they do not provide sufficient guidance or specificity as to how to execute that plan"); *National Recovery Technologies*, 166 F.3d at 1198 (stating that patent-in-suit "recognizes a specific need… and suggests a theoretical answer to that need. It provides a starting point from which one of skill in the art can perform further research in order to practice the claimed invention, but this is not adequate to constitute enablement"). The instant specification does not describe the claimed invention in terms that will "enable any person skilled in the art… to make and use" the invention commensurate in scope with the claims. At most, the specification will enable a person of ordinary skill in the art to attempt to discover how to practice the claimed invention.

Applicant is critical of the art of Rudikoff et al, Paul and Colman cited by the examiner, stating that the references are antiquated and do not adequately reflect the state of the art at the time of filing and applicant points out that the antibody art has evolved since 1982. Applicant also cites Peterson N. C. (ILAR J., 46(3):314-319, 2005), who states that the smallest functional unit of an antibody is a CDR peptide….which varies from as few as eight to twenty amino acids. Applicant argues that Rudikoff makes clear that not all substitutions need not and probably do not affect antigen binding and as many as eight or nine substitutions may occur in the hypervariable regions with no significant effect on hapten affinity or specificity. Applicant also argues that Paul and Colman support applicants' position. Applicants' arguments have been fully considered but are not found persuasive. The examiner agrees that the state of

the art has evolved since 1982, however, it remains unpredictable even in the current state of the art as to where amino acid changes can occur in an antibody structure and yield predictable results on binding. Applicant has previously acknowledged that the specification contemplates, though does not exemplify functional equivalents of the antibody produced by mutation, deletion and/or insertion within the variable regions or in the CDRs and assayed by techniques in the instant application. The specification does not enable the genus because where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one particular species, what other species will work. See MPEP 2164.03. The art also points out that changing the complementary determining regions is a hit and miss proposition and even minor changes in the amino acid sequences of heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidence by Rudikoff et al (Proc. Natl. Acad. Sci. USA, 79:1979-1983, 1982; cited on PTO-892 mailed 6/14/2006). Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma antibody resulted in the loss of antigen-binding function. Similarly, Colman P. M. (Research in Immunology, 145:33-36, 1994, cited on PTO-892 mailed 6/14/2006) teaches that even a very conservative substitution may abolish binding or may have very little effect on the binding affinity (see pg. 35, top of left column and pg. 33, right column). Applicant points out that Colman states: point mutations accumulating within the variable domains of antibody heavy and light chains are associated with increasing affinity of the antibody for antigen. Again, the examiner is not arguing that point mutations within the variable domains may not increase antibody affinity, the examiner is arguing that one of skill in the art could not predict in

advance which of the numerous amino acid substitutions, deletions and insertions and combinations thereof would result in an antibody that retains the binding characteristics of the parental antibody. Again, while many changes are theoretically possible, the art does not recognize predictable substitutions of individual CDR amino acids or combinations of CDR mutations that bind the same antigen, nor the deletion or insertion of amino acids in the variable regions or the CDRs as broadly embraced by the claims (i.e., 90% identity). The issue remains the description of the claimed antibody variants and guidance and direction of the specification for the claimed variants. With respect to Peterson, while Peterson acknowledges that a CDR is the smallest functional unit of an antibody, Peterson also points out that "an antibody uses multiple CDRs to bind an epitope and peptides lack three-dimensional structure, antibody based peptides have significantly less affinity than their multivalent parental antibodies". (see pg. 315, 1st col.). Further, Peterson reviews that the general strategy for "humanizing" antibodies involves the substitution of all six CDRs from a rodent antibody that binds an antigen of interest, and that all six CDRs are involved in antigen binding (see entire document, but especially Figures 1-3). Thus, the state of the art recognized that it would be unpredictable that a specific antibody comprising an antibody variable region but comprising less than all six CDRs of a parental antibody, or having at least 90% sequence identity to the heavy and/or light chain variable regions of a parent antibody with a desired specificity would retain the antigen-binding function of the parental antibody.

Applicant argues that Paul discloses that many aspects of an antibody molecule contribute to overall antigen binding specificity, including CDR length, sequence composition, localization in proximity to boundary regions, CDR backbone trajectory, CDR looping, the VH:VL dimer interface, as well as "weak interactions" between the epitope and paratope. Applicants' arguments have been fully considered but are not found persuasive. The examiner agrees that in addition to amino acid sequence, there are numerous other molecular interactions that influence antibody plasticity, which merely underscores the complexity and unpredictability in the art and exemplifies the numerous technical considerations that one of skill in the art has to consider in making

and using the claimed variants. The instant specification does not attempt to address the many aspects of an antibody molecule that contribute to overall antigen binding specificity including CDR length, sequence composition, localization in proximity to boundary regions, CDR backbone trajectory, CDR looping, the VH:VL dimer interface, as well as "weak interactions" between the epitope and paratope, all of which are encompassed by applicants' claims as pointed out at pg. 19 of the response. The examiner maintains that Paul (Fundamental Immunology, 3rd Edition, 1993, pp 292-295, PTO-892 mailed 6/14/2006) teaches that an intact antigen-binding site of antibodies routinely requires the association of the complete heavy and light chain variable regions of an antibody each of which consists of three CDRs or hypervariable regions presented in a specific order, which provide the majority of the contact residues for the binding of the antibody to its target epitope. Further, applicants' criticism of Rudikoff, Paul and Colman as antiquated references and hence, not particularly germane to the present enablement issue is curious in view of applicant's arguments that the references actually support applicants' position.

With respect to Patti et al (cited on PTO-892 mailed 6/14/2006), applicant sates that the examiner omitted amino acid 113 from SEQ ID NO:8 in conducting the comparison and the actual identity is 90.3%. Applicant also states that there is no support for the examiner's conclusion that Patti's 12-9 antibody does not specifically bind CD33. Applicant's arguments have been fully considered but are not found persuasive. Regardless of the inclusion of amino acid 113 of SEQ ID NO:8, the identity as noted by applicant is still at least 90% as embraced by the claims (e.g., see claim 6). Thus, it remains that Patti et al provide evidence of an embodiment within the broad scope of the claims that binds the ClfA protein. While applicant speculates that there is nothing in Watkins to indicate that the antibody does not bind CD33, similarly, there is nothing to indicate that it would bind CD33. Based on the facts presented by Patti, the antibody binds the ClfA protein from *Staphylococcus aureus*.

With respect to claims 1-2, 4, 7, 10 and 13 as currently amended as well as claims 3, 5-6, 8-9, 11-12, 14-16 and claims that depend therefrom recite "an amino acid sequence" of SEQ ID NO:X, which as stated in the previous Office Action still reads

upon fragments of the recited variable regions, fragments of a single CDR or fragments of a single framework region (e.g., FR1) since two amino acids of SEQ ID NO:7, for example, is merely one interpretation of "an amino acid sequence" of SEQ ID NO:7. Again, Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed antibodies in a manner reasonably correlated with the scope of the claims, broadly including less than all six CDRs of mouse monoclonal antibody My9-6 (i.e., SEQ ID Nos:1-6), or comprising a heavy and/or light chain variable region(s) having "an amino acid sequence" of SEQ ID NO:7 and/or 9, or of SEQ ID NO:8 and/or 10, respectively, or having "an amino acid sequence" that is 90-95% identical to SEQ ID Nos:7 and/or 8, or 90-95% identical to SEQ ID Nos:9 and/or 10, respectively, or improved antibodies comprising any number of amino acid substitutions, deletions or insertions in the variable regions of SEQ ID Nos:7 and/or 8 or SEQ ID Nos:9 and/or 10. Without such guidance, the changes which can be made in the protein's structure and still maintain antigen-binding function is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F, 2d 1200, 18 USPQ 1016 (Fed. Cir. 1991) at 18 USPQ 1026 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986).

In view of the lack of the predictability of the art to which the invention pertains as evidenced by Paul W. E., Rudikoff et al, Colman, and Patti et al, the lack of guidance and direction provided by applicant, and the absence of working examples, undue experimentation would be required to practice the claimed antibodies, or antibodies comprising just any mutations, deletions and/or insertions wherein the antibodies bind CD33 or have increased affinity for CD33 with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed antibodies and absent working examples providing evidence which is reasonably predictive that the claimed antibodies bind CD33, commensurate in scope with the claimed invention.

17. Claims 1-2 are objected to in the recitation "having an amino acid sequences", which is grammatically incorrect

Appropriate correction is required.

18. No claims is allowed.

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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/David J. Blanchard/
Primary Examiner, A.U. 1643